UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,399	11/02/2001	Caili Wang	13403.0005.NPUS00	8585

21971 7590 03/16/2005

WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 943041050

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,399	WANG ET AL.	
	Examiner	Art Unit	
	Gerald G. Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,10-20,41,42,45,47-54,56,57,59-62 and 64-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,10-12,18,41,42,45,47-54,56,57,59-62 and 64-76* is/are rejected.

7)☒ Claim(s) *13-17,19 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 November 2001 and 17 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/19/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Receipt is acknowledged of an amendment, filed on 11/19/2004, in which several claims were cancelled (claims 2-4, 8-9, 21-40, 43-44, 46, 55 and 63) and in which several claims were amended (claims 1, 5-7, 19-20, 41, 60-62, 64-66, 69, 72, 74 & 75). Claims 1, 5-7, 10-20, 41-42, 45, 47-54, 56-57, 59-62 and 64-76 are pending in the instant Office action.

Any rejection of record in the previous Office action not addressed herein is withdrawn. This action is not final as there are new grounds of rejection recited herein that were not necessitated by applicants' amendment of the claims in the response filed on 11/19/2004.

Information Disclosure Statement

Receipt is acknowledged of an information disclosure statement (IDS) filed on 11/19/2004. The signed and initialed PTO Form 1449 has been mailed along with the instant action.

Claim Objections

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Amended claim 1, upon which claim 5 is dependent, already states that the outer surface proteins are the outer surface proteins of a phage particle.

Claim 7 is objected to because of the following informalities: the phrase "wherein in the outer-surface sequences are selected from" is grammatically incorrect. The word "in" should be deleted from the cited phrase. Appropriate correction is required.

Claim 45 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Amended claim 41, upon which claim 45 is dependent, already states that the outer surface proteins are the outer surface proteins of a phage particle.

Claim 61 is objected to because of the following informalities: the phrase "according to method of claim 60" is grammatically incorrect. The word "the" should be inserted prior to the word "method" in the cited phrase. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 41-42, 45, 47-53, 56, 59 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Claim 41 is vague and indefinite in that the metes and bounds of the phrase "producing a polypeptide within or on the outer surface of a phage particle" are unclear in view of the way in which the polypeptide is displayed on the surface of the particle. Upon reading the specification, and in view of how the expression system that is claimed works, it does not appear one would

produce a protein that is incorporated "within" the phage particle. As described in the specification and recited in claim 41, the polypeptide would necessarily be displayed on the outer surface of the phage particle and would not be found "within" the particle.

Claim 61 is vague and indefinite in that it is unclear whether or not the claimed polypeptide must be displayed on the outer surface of a phage particle according to the method of claim 60 or whether the claim encompasses fusion proteins that can be displayed on the surface of a protein according to the method of claim 60. Claim 61 is directed to a protein and not to the phage particle that displays the protein. Because the method of claim 60 does not necessarily utilize a covalent linkage for display of the exogenous protein, and because the claim is directed to the protein, it is not clear whether the claim is limited to proteins actually in contact with the phage particle or further includes proteins that *can* be displayed on the particle. It would be remedial to amend the claim language to clearly indicate whether or not the protein encompassed by the claim is necessarily attached to the phage particle.

Claim 76 is vague and indefinite in that it is unclear whether the term "functional motif thereof" necessarily applies to all members of the Markush group, or only to one or a few of the members.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Many of the rejected claims are directed to an adapter-directed display system for displaying an exogenous polypeptide on the outer surface of a phage particle (e.g. Claim 1). The system comprises a first expression vector that comprises a sequence encoding the exogenous protein fused in-frame to a first adapter sequence, "wherein the vector is devoid of outer-surface sequences encoding functional outer-surface proteins of the phage particle." The system also comprises a helper vector that comprises nucleotide sequences encoding outer-surface proteins necessary for packaging the phage particle wherein at least one of the outer-surface proteins is fused in-frame with a second adapter. When expressed in an appropriate host cell, interaction between the first and second adapters results in display of the exogenous polypeptide on the surface of the phage particle (e.g. Claim 1). The adapters can mediate homodimerization or heterodimerization of the two fusion proteins (Claims 10 and 12). Homodimeric adapters can be two cysteine residues that form a disulfide linkage between the two fusion proteins (e.g. Claim 11). Some of the rejected claims are directed to the use of the system to display a polypeptide on the surface of a phage particle (e.g. Claim 60) and to use of a library of such particles to obtain a polypeptide having a desired property (e.g. Claim 72). Some of the rejected claims are directed solely to the first expression vector of the system, "wherein the vector is devoid of outer-surface sequences encoding functional outer-surface proteins of the phage particle." (e.g. claim 41). Some of the rejected claims are directed to a phage particle displaying on its outer surface a fusion polypeptide wherein the fusion polypeptide comprises the polypeptide to be displayed fused in-frame with a first adapter. Display of the fusion polypeptide on the surface of the phage particle is mediated via interaction with a surface protein of the phage coat that comprises a second adapter sequence (e.g. claim 62). Claim 61 is directed to a polypeptide displayed on the

outer surface of a phage particle according to the method of claim 60 (which uses the adapter-directed display system recited in claim 1 to produce chimeric phage displaying an exogenous protein).

The specification defines the concept of a "functional outer-surface protein" as follows:

> **By "functional" is meant that the encoded outer-surface proteins retain the ability to facilitate or direct the genetic package to assemble the polypeptide of interest onto its outer surface.(see page 36, paragraph 114).**

Thus, an expression vector encoding a fusion protein comprising a portion of a surface protein that is necessary for infectivity of a chimeric phage particle displaying the fusion protein (e.g. a gIII fusion protein) would not be excluded based upon the limitation "wherein the vector is devoid of outer-surface sequences encoding functional outer-surface proteins of the phage particle" unless that fusion is required to direct or facilitate interaction of the fusion protein with the phage particle.

The language of claim 61, "[a] polypeptide displayed on the outer surface of a phage particle according to the method of claim 60" is interpreted to not be limiting to a polypeptide that is actually physically present on the phage particle produced according to the method of claim 60 (e.g. see the 112 2nd paragraph rejection above). Rather, the claim is interpreted to encompass fusion proteins comprising an adapter that would allow them to be displayed on a particle made according to the method of claim 60. This interpretation is based on the fact that the claim is not directed to the entire particle, but is only directed to the fusion protein. Since the polypeptide displayed on the outer-surface of the phage particle according to claim 60 is not necessarily covalently linked to the particle, one can reasonably interpret the language as being directed to the polypeptide and excluding the phage particle.

Claims 62 & 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Krebber et al (FEBS Letters, 1995, Vol. 377, pages 227-231; see the entire document). **This rejection is maintained for reasons of record in the Office action mailed on 5/18/2004 and repeated below.**

Krebber et al teach a filamentous phage display system where two different proteins are operatively linked to different portions of the gIII protein such that infectivity of the phage is restored upon non-covalent interaction of the two fusion proteins such that a functional gIII-chimera is displayed on the surface of the phage (e.g. Figure 1). In this construction, both of the gIII fusion proteins are encoded by the same filamentous phage. Krebber et al describe competition between multiple cognate and noncognate gIII fusions (e.g. Table 3).

Response to Arguments

Applicant's arguments filed 11/19/2004 have been fully considered but they are not persuasive. The response essentially argues that the Krebber et al reference does not teach the specific, two vector adapter-directed display system as is recited in claim 1.

With regard to claims 62 and 64, this argument is not persuasive in that the claims do not recite the functional limitations that are recited in claim 1. Claim 62 is directed to a phage particle comprising on its outer surface a fusion polypeptide, the fusion polypeptide comprising a polypeptide sequence to be displayed that is fused in-frame with a first adapter (e.g. an amen-terminal fragment of gIII fused to an adapter sequence). The first adapter, when expressed in a suitable host cell, mediates the display of the fusion polypeptide via pairwise interaction with a second adapter that is linked to an outer-surface protein. The particles taught by Krebber et al comprise a first fusion polypeptide comprising the amino-terminal portion of the gIII protein to

an exogenous protein that is non-covalently bound to the phage particle via the interaction of the exogenous protein with a second fusion protein that comprises the C-terminal portion of gIII fused to a ligand for the exogenous protein. In the examples taught by Krebber et al, the amino-terminal portion of the gIII protein is displayed via this non-covalent interaction to yield an infectious particle.

Claims 41-42, 45, 48, 56, 59, 62 & 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Duenas et al (FEMS Microbiology Letters, 1995, Vol. 125, pages 317-322; see the entire reference) or Borrebaeck (U.S. Patent No. 6,027,930 A; see the entire patent; submitted on the 5/20/2002 IDS as reference #36). **This is a new rejection.**

Both references are directed to the same set of experiments featuring an improved helper vector for the display of chimeric proteins on chimeric filamentous phage particles that are used in methods for selection and amplification of phages (termed SAP by the authors of the Duenas et al article). In the phage display methods taught by the two references, a first expression vector is used to express a fusion protein comprising the protein to be displayed (i.e. the amino-terminal portion of the phage gIII protein required for infection fused to an Fab fragment that specifically binds hen egg lysozyme protein (HEL) (e.g. Examples 2-3, columns 5-6 of the '930 patent). The protein to be displayed (i.e. the portion of the phage gIII protein that mediates infection) is displayed on the chimeric phage particle due to the interaction of the Fab-adapter domain of the first fusion protein with the adapter domain of an HEL-gIII fusion protein incorporated into the phage particle.

It is noted that the gIII fragment of the Fab-gIII fusion taught by the two references is not required to direct or facilitate the binding of the fusion protein to the surface of the chimeric phage and is thus not excluded by the limitation "wherein the vector is devoid of outer-surface sequences encoding functional outer-surface proteins of the phage particle". However, with regard to this particular rejection, it would be remedial to amend the claims to include the limitation, as is explicitly recited in claim 1, that the protein that is displayed due to the interaction between the first and second adapters is an "exogenous protein" (i.e. a non-phage protein) that is displayed according to the method of claim 60.

Claims 1, 5-7, 10-11, 18, 41-42, 45, 47, 54, 56-57, 59-62 & 64-76 rejected under 35 U.S.C. 102(a) as being anticipated by Lohning et al (WO 01/05950 A2; cited as reference #64 in the IDS submitted 5/20/2002; see the entire reference). **This is a new rejection.**

Lohning et al teach novel methods for displaying polypeptides on the surface of bacteriophage particles using disulfide bonds to link the displayed polypeptide to the surface of the phage (e.g. Abstract). The PCT application teaches several different vectors for expression of heterologous polypeptides utilizing an unpaired cysteine residue recombinantly introduced to the polypeptide such that the modified polypeptide can form a disulfide bond with at least one phage coat protein comprising a cysteine residue. For example, the vectors pMorhpX7-hag2-LHC and pMorhpX7-hag2-LHC comprise sequences encoding a single chain antibody fragment directed against a peptide from influenza virus hemagglutinin (scFv-hag2) fused in-frame with a linker peptide (PGGSG), a 6-His peptide and a cysteine residue (e.g. Figure 1; pages 23-26, Example 1). In the first working example, the scFv-hag2/LHC polypeptides are expressed in

cells infected with a replication-defective helper phage (VCSM13) and chimeric phage isolated which display the scFv-hag2/LHC polypeptides on the surface of the phage. That the scFv-hag2/LHC polypeptides are attached to the surface of the phage through disulfide bonds with cysteine residues within proteins on the surface of the phage is demonstrated by the observation that in ELISA experiments with the hag2 antigen, retention of chimeric phage was lost upon incubation with the reducing agent DTT (e.g. Figure 5). In this example, the endogenous phage proteins comprising an accessible cysteine residue that forms a disulfide bond with the fusion protein can necessarily be considered as being "fused in-frame with a second adapter".

The PCT application teaches further examples wherein a modified gIIIc protein is provided from a second expression vector that encodes a gIII protein, fragment thereof, where a terminal cysteine residue has been added exogenously (e.g. Figure 6a; pages 26-27). In these examples, the interaction of the displayed polypeptide with the phage particle can presumably be between the unpaired cysteine residue in the modified gIIIc protein provided in trans and the unpaired cysteine residue of the first fusion protein.

It is noted that the scFv-hag2/LHC polypeptides taught by the Lohning et al PCT application also read on claim 61 in the sense that if one were to prepare an outer-surface 2nd adapter fusion protein according to claim 1 with the appropriate adapter (e.g. the hag2 antigen fused to gIII), one would be able to display the polypeptide on the surface of a phage particle according to the method of claim 60. As indicated above, claim 61 is not taken to be limited to those embodiments where the protein is actually attached to the phage particle.

Claims 1, 5-7, 12, 18, 41, 45, 48, 51, 54, 56-57, 59-62, 64-67, 69 are 71-76 are rejected under 35 U.S.C. 102(a) as being anticipated by Zucconi et al (Journal of Molecular Biology, 2001, Vol. 307, pages 1329-1339; reference submitted in the IDS filed 11/19/2004; see the entire reference). **This is a new rejection.**

Zucconi et al teach methods of selecting ligands by panning cDNA domain libraries displayed as fusion proteins with capsid protein D on phage λ (e.g. Abstract). In one set of panning experiments a fusion protein (GST-Syn) comprising a fragment of the proline-rich domain (PRD) of synaptojanin 1 and glutathione S-transferase (GST) was expressed and immobilized to a glutathione-Sepharose solid support. This affinity resin was panned with cDNA libraries from human brain whose products were displayed on the surface of phage λ as fusion proteins with gpD (e.g. page 1331, column 2). Several phage displaying different ligands for the synaptojanin 1 PRD domain were obtained and characterized with regard to their amino acid sequence. Sequence alignment of the obtained clones indicated that six classes of SH3 domain and one WW domain were obtained. In these experiments, the GST-Syn fusion protein can be considered as the fusion protein encoded by the expression vector of part (a) of claim 1 in that the PRD domain serves as an adapter that allows the "display" of the GST protein. The GST protein in this case has the desirable property of binding glutathione. Zucconi et al teach further experiments where different GST fusion proteins comprising peptide motifs from within the synaptojanin 1 PRD domain were used as bait for filamentous phage displaying random nonapeptides fused to the major coat protein pVIII (e.g. page 1333). The expression vectors used to express the various GST fusion proteins taught by Zucconi et al were not disclosed as

comprising any phage outer-surface sequences encoding functional outer-surface proteins of the λ particle, nor would there be any reason to expect such sequences to be present.

It is noted that in claim 60, there is no explicit recitation that the components of the adapter-directed display system of claim 1 are introduced into the same cell. For example, the phrase "transcribed and translated in a suitable host cell" can be interpreted to encompass embodiments where the different vectors are expressed in different cells of the same type (e.g. *E. coli*).

Conclusion

Claims 1, 5-7, 10-20, 41-42, 45, 47-54, 56-57, 59-62 and 64-76 are pending in the instant application. Claims 1, 5-7, 10-12, 18, 41, 42, 45, 47-54, 56, 57, 59-62 and 64-76 are rejected. Claims 10-17 and 19-20 are objected to as being dependent upon a rejected claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G. Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

ggl

GERRY LEFFERS
PRIMARY EXAMINER